REMARKS

I. Claims in the Case

Claims 13-15, 24, 32-40, 60, 62-63, 67, and 100 have been amended. Claims 1-4, 10, 45-59, and 85-96 have been cancelled and claims 101-108 added. Claims 5-9, 11-44, 60-84, and 97-108 are currently pending, of which claims 6-9, 16-19, 23, 25-31, and 76-84 are withdrawn.

The amendments to the preamble of claims 13 and 60 are made to broaden these claims and simplify their interpretation.

II. Claim Objections

The Action, on page 4, objects to claims 13 and 60 based on certain informalities, which have now been corrected.

Applicants note the Action's concern with respect to allegedly duplicate claims.

III. Rejection of Claims Under 35 U.S.C. 112, 1st Paragraph

The Action next rejects claims 11-14, 20-22, 24, 32-62, 64-75 and 85-100 on the basis of 35 U.S.C. 112, 1st paragraph, for reasons discussed and addressed below. Applicants respectfully traverse.

With respect to claim 13 and claims depending therefrom, the Action posits that there is insufficient written description in the specification as filed to support the claim language "overexpression relative to a control adenovirus vector that has the E3 structure of *dl*309 but otherwise has the same genetic structure as the overexpressing vector."

In response, Applicants traverse and must disagree with certain of the bases set forth for the Action's rejections. While it is agreed that *dl*309 does not "otherwise" have the "same genetic structure" as KD1, it ***does*** "otherwise" have the same genetic structure as GZ1 and GZ3,

and that comparison is shown in Figure 2. Similarly, the KD vectors "otherwise" have the same genetic structure as *dl*01/07, which comparison is also shown in Figure 2. However, Applicant's agree that the language would be confusing in the context of ADP-overexpressing vectors where the overexpression is achieved in ways other than E3 region modification.

Accordingly, Applicants are amenable to identifying language that the Examiner would find acceptable. Unfortunately, the Examiner has not made any suggestions as to what would be acceptable. For this reason, Applicants amend claim 13 and also provide new claims 101 and 102 with other alternatives for the Examiner to consider.

Amended claim 3 now recites, simply, "overexpression relative to *dl*309." This is a very straightforward claim and is directly supported by Figure 2 with respect to the exemplary vectors set forth in the specification, the KD series and the GZ series. The Examiner is apparently of the position that relying on disclosure relating to the KD and GZ vectors in this regard cannot be generalized to all vectors covered by the claims. However, Applicants disagree: The specification makes it clear, at page 5, lines 18-22, that the inventors contemplate that "overexpressing ADP" means overexpressing relative to "adenoviruses expressing wild-type levels of ADP." At page 12, lines 18-21, the specification notes that "overexpression" of ADP means overexpression relative to previously known adenoviruses. Then, in Example 1, the specification proceeds to test the 4 exemplifying adenoviruses against a panel of previously known adenoviruses, and demonstrated overexpression. The previously known adenoviruses tested included *dl*309, *dl*01/07, *dl*1520 (a.k.a. ONYX-015), *pm*734.1. See page 24. Accordingly, it is submitted from the tests shown in Example 1, in light of the general discussion from the other portions of the specification, that previously known viruses such as *dl*309 were intended to be a general "measuring stick" for overexpression.

It is specifically noted that on page 25, lines 28-30, the specification characterizes Ad5, *dl*309 and *dl*01/07 as "viruses expressing wild-type amounts of ADP."

If the Examiner has other suggestions that would be acceptable, he is respectfully requested to make such suggestions of record. Additionally, the Examiner is requested to consider the language of new claims 101-102 in this regard.

The Action next rejects claim 32, stating that Figure 2 and Example 2 do not support the recited assays as a means of determining overexpression. Applicants traverse.

With respect to cell lysis assay, in considering the cell lysis assay, the specification analyzes the results of that assay by observing that the assay shows that "over-expression of ADP increases the rate of cell lysis." Page 25, lines 18-21.

Similarly, with respect to the virus release assay, the specification shows that the assay is capable of distinguishing between viruses "which overexpress ADP" and those "expressing wild-type amounts of ADP." Page 25, lines 28-30.

With respect to the cell spreading assay, the specification uses the assay to measure the ability of viruses to lyse cells and spread to newly infected cells and demonstrates "the potency of ADP in mediating ... virus spread in A549 cells." Page 26, lines 5-6.

The Examiner's reliance on the *Purdue Pharma* case is misplaced. In *Purdue Pharma*, the limitation at issue was the so-called C_{max}/C_{24} ratio which was used in the claims in an attempt to define the class of agents that the claim covered. There, the C_{max}/C_{24} ratio was not discussed at all, but merely employed *ex post facto* to characterize two formulations. Nowhere in the patent specification was it stated that the C_{max}/C_{24} ratio was intended to be a distinguishing characteristic, with the court characterizing the C_{max}/C_{24} ratio as "...a characteristic that is not discussed even in passing in the disclosure ..."). 56 U.S.P.Q.2d at 1487..

In contrast, the issue here is the "overexpressing" language and how to interpret that language. There is no question that the specification identifies "overexpression" of ADP as a central focus of the invention, and it is identified throughout the specification as a desirable quality in virtually all embodiments. The question is merely how does the specification teach to measure overexpression, and there are four examples of how to measure overexpression given in Example 1. The Example in no way implies that these four methods are only applicable to KD1, KD2, GZ1 and GZ3 – on the contrary, the specification nowhere says that ADP overexpression is only desirable for these four vectors, and the examples merely provide an example as to how one might proceed to measure ADP expression.

The Action next rejects claim 60, alleging that the specification does not provide support for including "more" than one of the indicated adenovirus modifications at a time. Applicants traverse this rejection as well. The Examiner's attention is directed to the specification at page 13, lines 2-8, particularly at line 5. Applicants agree with the Action that this excerpt presents these four characteristics as alternatives. However, it also presents these characteristics as cumulative and combinable, particularly in light of the fact that the specification specifically employs the inclusive connector "and" when listing the possible elements. See page 13, line 5.

Next, with respect to claim 100, the claim has been amended as suggested.

IV. Rejection of Claims Under 35 U.S.C. 112, 2nd Paragraph

The Action next rejects claims 13-15, 20-22, 24, 32-44, 62, 63 and 67 under 35 U.S.C. 112, 2nd paragraph, for inappropriate antecedent basis and slightly improper phraseology. Applicants have amended the claims in the manner suggested, which should adequately address

the concerns. It is submitted that none of these amendments in any way alter the scope of the claims.

V. Rejection of Claims over the Art

The 102(e) Rejections

The Action next rejects claims 10-13, 32-44, 60, 61, 68, 69, 72-75, 85-87, 89-91 and 94-99 under 102(e) as anticipated by either the Henderson *et al.* or Little *et al.* patent. Applicants respectfully traverse. In responding to the rejection, Applicants will provide separate arguments with respect to various claims and will group the claims accordingly. Furthermore, the arguments and evidence provided in Applicants earlier responses, particularly that of 6/19/03, are incorporated herein by reference.

The "Overexpresses ADP" Claims 11- 13, 32-44 and 101-106

Applicants will first address the anticipation rejection with respect to the "overexpressing ADP" claims that have been rejected, which, of those now active, includes claims 11-13 and 32-44 (and newly added claims 101-106).

Since this is an anticipation rejection, the Examiner must demonstrate that each and every element of the claims is either explicitly or necessarily disclosed in the allegedly anticipatory art. That has not been done here. Each of the "overexpresses ADP" claims require *overexpression* of ADP and there is no teaching anywhere in either Henderson or Little that the vectors they describe overexpress ADP, as that term is used.

On the contrary, both patents teach that CN751 expresses about the same amount of ADP as does wild-type adenovirus. This can be seen in Henderson, for example, at col. 49, lines 6-8. Here it is stated that CN751 kills cells more efficiently than an ADP-minus control, but about the

same as an ADP-positive control, Rec700. See also Little *et al.* patent at col. 40, lines 24-26. We know from the present applicant's specification that cell killing is a good measure of ADP expression. See Example 2.

The Action's principal response to this argument is that Applicant has allegedly "indicated on the record (response filed 1/10/02, page 7) that CN751 would be expected to overexpress ADP." Applicant denies that such a representation was made – the statement referred to by the Examiner was a recitation of the pending rejection that failed to fully attribute the statement to the Examiner. In any event, such a statement does not reflect reality of what Little and Henderson disclose, and the reality is that neither reference teaches overexpression of ADP.

The Action appears to further argue, in the last paragraph on page 11 of the Action, with respect to claims depending from claim 13, that Henderson/Little teach placing ADP under control of a heterologous promoter (tissue specific or viral promoter), or inclusion of multiple copies of ADP, "would be expected to result in overexpression compared to *dl*309. In response to this argument, Applicant states that it is unclear what art the Examiner is relying on for this proposition and how this art relates to overexpression of ADP. Accordingly, the Examiner is respectfully requested to make such art of record so that Applicants might analyze and respond to it. If the Examiner is relying on his own personal knowledge, such knowledge should be made of record by means of affidavit or declaration. See 37 C.F.R. § 1.104(d)(2).

For the foregoing reasons, it is evident that the Action fails to make out a *prima facie* anticipation of the ADP overexpression claims. (For the sake of completeness, Applicants also incorporate by reference here the comments set forth below with respect to the remaining claims alleged to be anticipated).

The Structural Claims – Claims 60, 61, 68, 69, 72-72, 85-87, 89-91 and 94-99

The Action further rejects structural claims 60, 61, 68, 69, 72-72, 85-87, 89-91 and 94-99 as anticipated by Henderson/Little, noting merely that these claims do not require overexpression of ADP.

In response, Applicants provide a supplemental declaration of the inventors that supplements the declaration filed 1/6/03 by demonstrating that shortly after KD1 was shown to overexpresss ADP (in studies conducted in May and June of 1997), it was tested in animals having tumors and shown to have antitumor activity. In the enclosed declaration, the inventors first note that in their earlier declaration they demonstrated that the adenovirus vector KD1 was constructed prior to March 3, 1997, and, in numerous studies that they conducted between 5/9/97 and 6/2/97, KD1 was shown to overexpress ADP. They then state that the supplemental declaration is being submitted to demonstrating that (1) prior to March 3, 1997, the inventors conceived of using ADP-expressing adenoviral vectors for treating cancer in patients, and that (2) shortly after March 3, 1997 an exemplary vector, KD1, was tested in an animal having cancer and shown to have anticancer activity.

The specifics of the declaration demonstrate that prior to March 3, 1997 the inventors conceived of the idea of using adenovirus vectors expressing the ADP gene as a therapeutic agent to treat cancer. This is shown, for example, in Exhibit B of the 1/6/03 declaration, at, for example, page 3, section B, and pages 4-8. The Exhibit B document is dated prior to March 3, 1997.

The inventors go on to show that on July 7, 1997, they sent KD1, dl1101/1107, dl309, and A549 cells to Dr. Jeffrey A. Whitsett at the Children's Hospital Medical Center, Division of Pulmonary Biology, Cincinnati, OH. A copy of the cover letter sent to Dr. Whitsett is attached

as Exhibit M. They state that Dr. Whitsett had agreed to test these vectors on our behalf in the A549 nude mouse model, in which A549 human lung carcinoma cells are used to establish tumors in nude mice following by injection of the various vectors to determine their anticancer efficacy. On September 16, 1997, the inventors received a report from Dr. Whitsett's colleague, Lee Zhang, indicating that "10^9 pfu of each of the viruses were injected into each established A549 tumor. 4 out of 6 tumors injected with KD1 showed slowed tumor growth while 2 out of 2 tumors injected with dl309 and 4 out of 4 injected with dl 1101/1107 continued to grow." A copy of this fax is attached as Exhibit N.

The inventors conclude that the foregoing studies conducted on their behalf demonstrated the successful use of KD1 in the treatment of cancer in an animal at least as early as September, 1997.

In case the Examiner seeks to raise any issue regarding diligence, which is highly unlikely, Applicants would refer the Examiner to page 9 of the 1/6/03 declaration which demonstrates continuous activity throughout the month of June, 1997, shortly after which, on July 7, 1997, the vectors were sent out for testing in animals.

The remaining matters raised by the Examiner have been adequately dealt with in previous responses, including:

- The Examiner states, on page 13, that "there is no nexus between Exhibit B and KD and GZ vectors. Applicants are unsure of the Examiner's position here, but are confident that an full and complete conception, diligence and reduction to practice of the subject matter of the claimed invention has been shown.
- The Examiner takes the position, at the bottom of page 13, that the vectors of Little/Henderson have additional features not found in Applicants vectors, such as

the use of tissue specific promoters to control the expression of essential genes, or the inclusion of multiple copies of genes, *etc.* Applicants response is that this is irrelevant, as Applicants have demonstrated the conception and reduction to practice of exemplary subject matter that meets the limitations of the pending independent claims. Applicants further refer the Examiner to the caselaw cited and explained in our previous response.

- The Examiner takes the position, at the bottom of page 14, that "conception of the means, i.e. the adenovirus vector, to overexpress ADP did not occur until after the priority dates" of the Little/Henderson patents. This is simply incorrect. The 1/6/03 declaration shows that at least KD1 was constructed prior to the Little/Henderson priority date.
- The Examiner lastly takes the position that the Declaration does not show prior possession of vector where ADP is overexpressed by other means, such as multiple copies or the use of a heterologous promoter. Applicants again refer the Examiner to the previously cited caselaw, which makes it clear that one need only demonstrate prior invention of one embodiment within the scope of a generic claim in order to demonstrate priority. See, *e.g.*, *In re Hostettler*, discussed at the bottom of page 19 of Applicants last response.

Accordingly, for the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the instant anticipation rejection.

The 103 Rejections

The Action next rejects claims 13, 20-22, 60 and 64-66 as obvious over Henderson/Little in light of Freytag. Henderson/Little is cited as above, whereas Freytag is alleged to teach

combination therapy using adenoviruses and chemotherapy and/or radiation. Applicants respectfully traverse.

Applicants incorporate by reference the arguments set forth in the anticipation section above with respect to Little/Henderson. First, with respect to independent claims 13 and 60, it is noted that Freytag adds nothing to the teachings of Little/Henderson that is relevant to the subject matter of these claims. If the Examiner is of a contrary opinion, he is respectfully requested to point out the relevance of Freytag with respect to cliam 13 or 60.

With respect to the dependent claims, Applicants note that Freytag merely discloses a so--called suicide gene adenovirus vector comprising the CD/HSV-1 TK gene. This suicide gene construct is specially constructed to be used with radiation and chemotherapy. There is no mention of an ADP gene or vectors employing the ADP gene or upregulated expression of ADP, and thus no motivation to employ radiation except in connection with vectors that bear the special suicide CD/HSV-1 TK gene construct. Accordingly, there is no basis for combining this reference with the ADP teachings of Little/Henderson to arrive at the invention of claims 13, 20-22, 60 or 64-66. Thus, no *prima facie* rejection has been established.

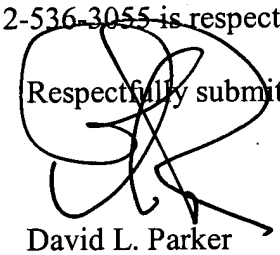
For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the instant obviousness rejection.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn because they are in condition for allowance. At the very least, Applicants request that the Examiner enter these amendments in order to place the case in better form for an appeal.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3055 is respectfully requested.

Respectfully submitted,



David L. Parker
Reg. No. 32,165
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 474-5201
(512) 536-4598 (facsimile)

Date: December 3, 2003